

Claims

1. A method for increasing endothelial cell Nitric Oxide Synthase activity in a nonhypercholesterolemic subject who would benefit from increased endothelial cell Nitric Oxide Synthase activity in a tissue comprising:
  - 5 administering to a nonhypercholesterolemic subject in need of such treatment a HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said tissue of the subject.
- 10 2. The method of claim 1, wherein the subject is nonhypertriglyceridemic.
- 15 3. The method of claim 1, wherein the subject is nonhyperlipidemic.
4. The method of claim 1, wherein the amount is less than an amount which alters the blood LDL cholesterol levels in the subject by 10%.
5. The method of claim 1, wherein the amount is sufficient to increase endothelial cell Nitric Oxide Synthase activity above normal baseline levels.
- 20 6. The method of claim 1, wherein the subject has a condition comprising an abnormally low level of endothelial cell Nitric Oxide Synthase activity which is chemically induced.
7. The method of claim 1, wherein the subject has an abnormally elevated risk of pulmonary hypertension.
- 25 8. The method of claim 1, wherein the subject has pulmonary hypertension.
9. The method of claim 1, wherein the subject has an abnormally elevated risk of an ischemic stroke.
- 30 10. The method of claim 1, wherein the subject has experienced an ischemic stroke.
11. The method of claim 1, wherein the subject is chronically exposed to hypoxic conditions.

12. The method of claim 1, wherein the subject has an abnormally elevated risk of thrombosis.

13. The method of claim 1, wherein the subject has thrombosis.

5 14. The method of claim 1, wherein the subject has an abnormally elevated risk of arteriosclerosis.

15. The method of claim 1, wherein the subject has arteriosclerosis.

10 16. The method of claim 1, wherein the subject has an abnormally elevated risk of myocardial infarction.

17. The method of claim 1, wherein the subject has experienced a myocardial infarction.

15 18. The method of claim 1, wherein the subject has an abnormally elevated risk of reperfusion injury.

19. The method of claim 18, wherein the subject is a transplant recipient.

20. The method of claim 1, wherein the subject has homocystinuria.

21. The method of claim 1, wherein the subject has a neurodegenerative disease.

22. The method of claim 21, wherein the neurodegenerative disease is Alzheimer's disease.

25 23. The method of claim 1, wherein the subject has CADASIL syndrome.

24. The method of claim 1, wherein the HMG-CoA reductase inhibitor is administered in an amount which is insufficient to alter blood cholesterol levels by more than 10%.

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26. The method of claims 1-25, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

27. The method of claim 26, wherein the endothelial cell Nitric Oxide Synthase substrate is 5 L-arginine.

28. The method of claim 26, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

10 29. The method of claim 28, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

15 30. The method of claims 1-25, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin and lovastatin.

15 31. The method of claim 30, wherein the HMG-CoA reductase inhibitor is lovastatin.

20 32. The method of claim 30, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

33. The method of claim 32, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

25 34. The method of claim 32, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

35. The method of claim 34, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

30 36. The method of claims 1-25, further comprising co-administering at least one different HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said tissue of the subject.

37. The method of claim 36, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

38. The method of claim 37, wherein the endothelial cell Nitric Oxide Synthase substrate is 5 L-arginine.

39. The method of claim 37, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

10 40. The method of claim 39, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

15 41. The method of claims 1-25, further comprising co-administering at least one different HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity.

42. The method of claim 41, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

43. The method of claim 42, wherein the endothelial cell Nitric Oxide Synthase substrate is 20 L-arginine.

44. The method of claim 42, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

25 45. The method of claim 44, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

30 46. A method for increasing endothelial cell Nitric Oxide Synthase activity in a subject to treat a nonhyperlipidemic condition favorably affected by an increase in endothelial cell Nitric Oxide Synthase activity in a tissue comprising:  
administering to a subject in need of such treatment a HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said

tissue of the subject.

47. The method of claim 46, wherein the amount is less than an amount which alters the blood LDL cholesterol levels in the subject by 10%.

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48. The method of claim 46, wherein the subject is nonhypercholesterolemic.

49. The method of claim 46, wherein the subject is nonhyperlipidemic.

10 50. The method of claim 46, wherein the amount is sufficient to increase endothelial cell Nitric Oxide Synthase activity above normal baseline levels.

51. The method of claim 46, wherein the subject has a condition comprising an abnormally low level of endothelial cell Nitric Oxide Synthase activity which is chemically induced.

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52. The method of claim 46, wherein the subject has an abnormally elevated risk of pulmonary hypertension.

53. The method of claim 46, wherein the subject has pulmonary hypertension.

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54. The method of claim 46, wherein the subject has an abnormally elevated risk of an ischemic stroke.

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55. The method of claim 46, wherein the subject has experienced an ischemic stroke.

56. The method of claim 46, wherein the subject is chronically exposed to hypoxic conditions.

57. The method of claim 46, wherein the subject has an abnormally elevated risk of thrombosis.

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58. The method of claim 46, wherein the subject has thrombosis.

59. The method of claim 46, wherein the subject has an abnormally elevated risk of arteriosclerosis.

60. The method of claim 46, wherein the subject has arteriosclerosis.

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61. The method of claim 46, wherein the subject has an abnormally elevated risk of myocardial infarction.

62. The method of claim 46, wherein the subject has experienced a myocardial infarction.

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63. The method of claim 46, wherein the subject has an abnormally elevated risk of reperfusion injury.

64. The method of claim 63, wherein the subject is a transplant recipient.

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65. The method of claim 46, wherein the subject has homocystinuria.

66. The method of claim 46, wherein the subject has a neurodegenerative disease.

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67. The method of claim 66, wherein the neurodegenerative disease is Alzheimer's disease.

68. The method of claim 46, wherein the subject has CADASIL syndrome.

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69. The method of claim 46, wherein the HMG-CoA reductase inhibitor is administered in an amount which is insufficient to alter blood cholesterol levels by more than 10%.

70. The method of claim 46, wherein the HMG-CoA reductase inhibitor is not fasudil, when the subject in need of such treatment has an abnormally elevated risk of an ischemic stroke.

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71. The method of claims 46-70, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

72. The method of claim 71, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

73. The method of claim 71, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

74. The method of claim 73, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

75. The method of claims 46-70, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin and lovastatin.

76. The method of claim 75, wherein the HMG-CoA reductase inhibitor is lovastatin.

77. The method of claim 75, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

78. The method of claim 77, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

79. The method of claim 77, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

80. The method of claim 79, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

81. The method of claims 46-70, further comprising co-administering at least one different HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said tissue of the subject.

82. The method of claim 81, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

83. The method of claim 82, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

84. The method of claim 82, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

85. The method of claim 84, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

86. The method of claims 46-70, further comprising co-administering a non-HMG-CoA reductase inhibitor agent that increases endothelial cell Nitric Oxide Synthase activity.

87. The method of claim 86, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

88. The method of claim 87, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

89. The method of claim 87, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

90. The method of claim 89, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

91. A method for reducing brain injury resulting from a stroke, comprising: administering to a subject having an abnormally high risk of an ischemic stroke, a HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the brain tissue of the subject.

92. The method of claim 91, wherein the HMG-CoA reductase inhibitor is administered in an amount which is insufficient to alter blood cholesterol levels by more than 10%.

93. The method of claim 91, wherein the subject is nonhypercholesterolemic.

94. The method of claim 91, wherein the subject is nonhyperlipidemic.

5 95. The method of claim 91, wherein the HMG-CoA reductase inhibitor is administered prophylactically.

10 96. The method of claim 91, wherein the HMG-CoA reductase inhibitor is administered acutely.

15 97. The method of claims 91-96, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin and lovastatin.

98. The method of claim 97, wherein the HMG-CoA reductase inhibitor is lovastatin.

15 99. The method of claims 91-96, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

100. The method of claim 99, wherein the endothelial cell Nitric Oxide Synthase substrate is  
20 L-arginine.

101. The method of claim 99, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

25 102. The method of claim 101, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

30 103. The method of claims 91-96, further comprising co-administering at least one different HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity.

104. The method of claim 103, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

105. The method of claim 104, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

106. The method of claim 104, further comprising co-administering an endothelial cell Nitric  
5 Oxide Synthase cofactor.

107. The method of claim 106, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

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108. The method of claims 91-96, further comprising co-administering at least one different HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide  
Synthase activity in said tissue of the subject.

109. The method of claim 108, further comprising co-administering a substrate of endothelial  
15 cell Nitric Oxide Synthase.

110. The method of claim 109, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

20 111. The method of claim 109, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

112. The method of claim 111, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

25 113. A method for treating pulmonary hypertension comprising:  
administering to a subject in need of such treatment a HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the pulmonary tissue of the subject, provided that the HMG-CoA reductase inhibitor is not a HMG-  
30 CoA reductase inhibitor.

114. The method of claim 113, wherein the subject is nonhypercholesterolemic.

115. The method of claim 113, wherein the subject is nonhyperlipidemic.

116. The method of claim 113, wherein the *rho* GTPase function inhibitor is administered prophylactically to a subject who has an abnormally elevated risk of developing pulmonary hypertension.

117. The method of claim 113, wherein the HMG-CoA reductase inhibitor is administered acutely to a subject who has pulmonary hypertension.

118. The method of claim 113, wherein the subject is chronically exposed to hypoxic conditions.

119. The method of claims 113-118, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin and lovastatin.

120. The method of claim 119, wherein the HMG-CoA reductase inhibitor is lovastatin.

121. The method of claims 113-118, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

122. The method of claim 121, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

123. The method of claim 121, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

124. The method of claim 123, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

125. The method of claims 113-118, further comprising co-administering at least one different HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity.

126. The method of claims 113-118, further comprising co-administering at least one different HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said tissue of the subject.

5 127. The method of claim 125, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

128. The method of claim 127, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

10 129. The method of claim 127, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

130. The method of claim 129, wherein the endothelial cell Nitric Oxide Synthase cofactor is

15 NADPH or tetrahydrobiopterin.

131. A method for treating heart failure comprising:  
administering to a subject in need of such treatment a HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the heart tissue of the subject, provided that the HMG-CoA reductase inhibitor is not a *rho* GTPase function inhibitor.

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132. The method of claim 131, wherein the subject is nonhypercholesterolemic.

25 133. The method of claim 131, wherein the subject is nonhyperlipidemic.

134. The method of claim 131, wherein the HMG-CoA reductase inhibitor is administered prophylactically to a subject who has an abnormally elevated risk of heart failure.

30 135. The method of claim 131, wherein the HMG-CoA reductase inhibitor is administered acutely to a subject who has heart failure.

136. The method of claims 131-135, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin and lovastatin.

137. The method of claim 136, wherein the HMG-CoA reductase inhibitor is lovastatin.

5 138. The method of claims 136, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

10 139. The method of claim 138, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

140. The method of claim 138, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

15 141. The method of claim 140, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

20 142. The method of claims 131-135, further comprising co-administering at least one different HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said tissue of the subject.

143. The method of claim 142, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

25 144. The method of claim 143, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

145. The method of claim 143, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

30 146. The method of claim 145, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

147. The method of claims 131-135, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

5 148. The method of claim 147, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

149. The method of claim 147, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

10 150. The method of claim 149, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

151. The method of claims 131-135, further comprising co-administering at least one different HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity.

15 152. The method of claim 151, further comprising co-administering an endothelial cell Nitric Oxide Synthase substrate.

20 153. The method of claim 152, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

154. The method of claim 152, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

25 155. The method of claim 154, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

30 156. A method for treating progressive renal disease comprising:  
administering to a subject in need of such treatment a HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the kidney tissue of the subject, provided that the HMG-CoA reductase inhibitor is not a *rho* GTPase

function inhibitor.

157. The method of claim 156, wherein the subject is nonhypercholesterolemic.

5 158. The method of claim 156, wherein the subject is nonhyperlipidemic.

159. The method of claim 156, wherein the HMG-CoA reductase inhibitor is administered prophylactically.

10 160. The method of claim 156, wherein the HMG-CoA reductase inhibitor is administered acutely.

161. The method of claims 156-160, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin and lovastatin.

15 162. The method of claim 161, wherein the HMG-CoA reductase inhibitor is lovastatin.

163. The method of claims 156-160, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

20 164. The method of claims 156-160, further comprising co-administering at least one different HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity.

165. The method of claims 156-160, further comprising co-administering at least one different 25 HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said tissue of the subject.

166. The method of claim 164, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

30 167. A method for increasing blood flow in a tissue of a subject, comprising administering to a subject in need of such treatment a HMG-CoA reductase

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inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the tissue of the subject.

168. The method of claim 167, wherein blood flow is increased in brain tissue.

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169. The method of claim 167 wherein the subject is nonhypercholesterolemic.

170. The method of claim 167, wherein the subject is nonhyperlipidemic.

10 171. The method of claim 168, wherein the subject is nonhypercholesterolemic.

172. The method of claim 168, wherein the subject is nonhyperlipidemic.

15 173. The method of claim 167, wherein the HMG-CoA reductase inhibitor is administered prophylactically.

174. The method of claim 167, wherein the HMG-CoA reductase inhibitor is administered acutely.

20 175. The method of claims 167-174, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin and lovastatin.

176. The method of claim 175, wherein the HMG-CoA reductase inhibitor is lovastatin.

25 177. The method of claims 167-174, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

30 178. The method of claim 177, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

179. The method of claim 177, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

180. The method of claim 179, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

5 181. The method of claims 167-174, further comprising co-administering at least one different HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity.

182. The method of claims 167-174, further comprising co-administering at least one different HMG-CoA reductase inhibitor in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in said tissue of the subject.

10 183. The method of claim 181, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

15 184. The method of claim 183, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

185. The method of claim 183, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

20 186. The method of claim 185, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

25 187. The method of claims 167-174, further comprising co-administering a second agent to the subject with a condition treatable by the second agent in an amount effective to treat the condition, whereby the delivery of the second agent to a tissue of the subject is enhanced as a result of the increased blood flow.

30 188. The method of claim 187, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

189. The method of claim 188, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

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190. The method of claim 188, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

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191. The method of claim 190, wherein the endothelial cell Nitric Oxide Synthase cofactor is  
5 NADPH or tetrahydrobiopterin.

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192. The method of claims 167-174, further comprising co-administering a second agent to the subject with a condition treatable by the second agent in an amount effective to treat the condition, whereby the delivery of the second agent to the brain of the subject is enhanced as a result of the increased blood flow.

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193. The method of claims 167-174, further wherein the tissue is brain and the second agent comprises an agent having a site of action in the brain.

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194. The method of claim 192, wherein the second agent is selected from the group consisting of analeptic, analgetic, anesthetic, adrenergic agent, anti-adrenergic agent, amino acids, antagonists, antidote, anti-anxiety agent, anticholinergic, anticolvulsant, antidepressant, anti-emetic, anti-epileptic, antihypertensive, antifibrinolytic, antihyperlipidemia, antimigraine, antinauseant, antineoplastic (brain cancer), antibessional agent, antiparkinsonian, antipsychotic, 20 appetite suppressant, blood glucose regulator, cognition adjuvant, cognition enhancer, dopaminergic agent, emetic, free oxygen radical scavenger, glucocorticoid, hypocholesterolemic, hollylipidemic, histamine H2 receptor antagonists, immunosuppressant, inhibitor, memory adjuvant, mental performance enhancer, mood regulator, mydriatic, neuromuscular blocking agent, neuroprotective, NMDA antagonist, post-stroke and post-head 25 trauma treatment, psychotropic, sedative, sedative-hypnotic, serotonin inhibitor, tranquilizer, and treatment of cerebral ischemia, calcium channel blockers, free radical scavengers - antioxidants, GABA agonists, glutamate antagonists, AMPA antagonists, kainate antagonists, competitive and non-competitive NMDA antagonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, sodium- and calcium-channel blockers, and 30 potassium channel openers.

195. The method of claim 193, wherein the agent having a site of action in the brain is selected

from the group consisting of analeptic, analgetic, anesthetic, adrenergic agent, anti-adrenergic agent, amino acids, antagonists, antidote, anti-anxiety agent, anticholinergic, anticolvulsant, antidepressant, anti-emetic, anti-epileptic, antihypertensive, antifibrinolytic, antihyperlipidemia, antimigraine, antinauseant, antineoplastic (brain cancer), antiofessional agent, antiparkinsonian, antipsychotic, appetite suppressant, blood glucose regulator, cognition adjuvant, cognition enhancer, dopaminergic agent, emetic, free oxygen radical scavenger, glucocorticoid, hypocholesterolemic, hollylipidemic, histamine H2 receptor antagonists, immunosuppressant, inhibitor, memory adjuvant, mental performance enhancer, mood regulator, mydriatic, neuromuscular blocking agent, neuroprotective, NMDA antagonist, post-stroke and post-head

10 trauma treatment, psychotropic, sedative, sedative-hypnotic, serotonin inhibitor, tranquilizer, and treatment of cerebral ischemia, calcium channel blockers, free radical scavengers - antioxidants, GABA agonists, glutamate antagonists, AMPA antagonists, kainate antagonists, competitive and non-competitive NMDA antagonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, sodium- and calcium-channel blockers, and

15 potassium channel openers.

196. The method of claim 187, wherein the second agent is selected from the group consisting of analeptic, analgetic, anesthetic, adrenergic agent, anti-adrenergic agent, amino acids, antagonists, antidote, anti-anxiety agent, anticholinergic, anticolvulsant, antidepressant, anti-emetic, anti-epileptic, antihypertensive, antifibrinolytic, antihyperlipidemia, antimigraine, antinauseant, antineoplastic (brain cancer), antiofessional agent, antiparkinsonian, antipsychotic, appetite suppressant, blood glucose regulator, cognition adjuvant, cognition enhancer, dopaminergic agent, emetic, free oxygen radical scavenger, glucocorticoid, hypocholesterolemic, hollylipidemic, histamine H2 receptor antagonists, immunosuppressant, inhibitor, memory adjuvant, mental performance enhancer, mood regulator, mydriatic, neuromuscular blocking agent, neuroprotective, NMDA antagonist, post-stroke and post-head

20 trauma treatment, psychotropic, sedative, sedative-hypnotic, serotonin inhibitor, tranquilizer, and treatment of cerebral ischemia, calcium channel blockers, free radical scavengers - antioxidants, GABA agonists, glutamate antagonists, AMPA antagonists, kainate antagonists, competitive and non-competitive NMDA antagonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, sodium- and calcium-channel blockers, and

25 potassium channel openers.

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197. The method of claim 192, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

5 198. The method of claim 197, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

10 199. The method of claim 197, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

200. The method of claim 199, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

15 201. The method of claim 193, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

202. The method of claim 201, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

203. The method of claim 201, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

25 204. The method of claim 203, wherein the endothelial cell Nitric Oxide Synthase cofactor is NADPH or tetrahydrobiopterin.

205. A method of screening for identifying a HMG-CoA reductase inhibitor for treatment of subjects who would benefit from increased endothelial cell Nitric Oxide Synthase activity in a tissue, comprising:

30 (a) identifying a HMG-CoA reductase inhibitor suspected of increasing endothelial cell Nitric Oxide Synthase activity, and

(b) determining whether or not the HMG-CoA reductase inhibitor produces an increase in endothelial cell Nitric Oxide Synthase activity *in vivo* or *in vitro*.

206. The method of claim 205, wherein the subject who would benefit from increased endothelial cell Nitric Oxide Synthase activity in a tissue has an abnormally elevated risk of an ischemic stroke or has experienced a stroke, and the increased endothelial cell Nitric Oxide Synthase activity is increased in brain tissue.

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207. A composition comprising a HMG-CoA reductase inhibitor and L-arginine.

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208. The composition according to claim 207, wherein the composition is a pharmaceutical composition.

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209. The composition according to claim 207, wherein the HMG-CoA reductase inhibitor and the L-arginine are in amounts effective to increase blood flow.

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210. The composition according to claim 207, wherein the HMG-CoA reductase inhibitor and the L-arginine are in amounts effective to increase blood flow in brain tissue.

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211. The composition according to claim 207, wherein the administration of said composition results in increased blood flow.

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212. The composition according to claim 207, wherein the administration of said composition results in increased blood flow to the brain.

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213. The method of claim 182, further comprising co-administering a substrate of endothelial cell Nitric Oxide Synthase.

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214. The method of claim 213, wherein the endothelial cell Nitric Oxide Synthase substrate is L-arginine.

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215. The method of claim 213, further comprising co-administering an endothelial cell Nitric Oxide Synthase cofactor.

216. The method of claim 215, wherein the endothelial cell Nitric Oxide Synthase cofactor is

NADPH or tetrahydrobiopterin.

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